

Table 4.1 Number of Subjects Reporting All-Causalities Adverse Events (12 week studies)

	Placebo N=685	50mg BID N=692	100mg BID N=664	200mg BID N=672	Naproxan N=656	P-Value*
Body System	N (%)	N (%)	N (%)	N (%)	N (%)	
APPLICATION SITE DISORDERS	5 (0.7)	5 (0.7)	12 (1.8)	6 (0.9)	2 (0.3)	0.576
AUTONOMIC NERVOUS SYSTEM DISORDERS	11 (1.6)	5 (0.7)	13 (2.0)	19 (2.8)	14 (2.1)	0.052
BODY AS A WHOLE-GENERAL DISORDERS	109 (15.9)	106 (15.3)	115 (17.3)	120 (17.9)	105 (16.0)	0.536
DEMA PERIPHERAL	8 (1.2)	14 (2.0)	12 (1.8)	25 (3.7)	15 (2.3)	0.026
ALLERGIC REACTION	0 (0.0)	0 (0.0)	3 (0.5)	7 (1.0)	1 (0.2)	0.048
CHEST PAIN	3 (0.4)	2 (0.3)	4 (0.6)	6 (0.9)	9 (1.4)	0.016
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	163 (23.8)	148 (21.4)	160 (24.1)	150 (22.3)	121 (18.4)	0.057
HEADACHE	140 (20.4)	115 (16.6)	129 (19.4)	110 (16.4)	90 (13.7)	0.003
ENDOCRINEDISORDERS	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	4 (0.6)	0.099
GASTRO-INTESTINAL SYSTEM DISORDERS	158 (23.1)	161 (23.3)	171 (25.8)	183 (27.2)	222 (33.8)	<.001
ABDOMINAL PAIN	21(3.1)	28(4.0)	29(4.4)	34(5.1)	37(5.6)	0.014
CONSTIPATION	11 (1.6)	10 (1.4)	14 (2.1)	17 (2.5)	35 (5.3)	<.001
DYSPEPSIA	53(7.7)	55(7.9)	54(8.1)	69(10.3)	79(12.0)	0.002
FLATULENCE	8(1.2)	16(2.3)	11(1.7)	10(1.5)	24(3.7)	0.018
VOMITING	3 (0.4)	6 (0.9)	9 (1.4)	10 (1.5)	9 (1.4)	0.049
HEARING AND VESTIBULAR DISORDERS	5(0.7)	6(0.9)	6(0.9)	5(0.7)	2(0.3)	0.350
HEARTRATE AND RHYTHM DISORDERS	4(0.6)	5(0.7)	3(0.5)	6(0.9)	6(0.9)	0.421
LIVER AND BILIARY SYSTEM DISORDERS	6(0.9)	5(0.7)	5(0.8)	5(0.7)	7(1.1)	0.722
METABOLIC AND NUTRITIONAL DISORDERS	14(2.0)	30(4.3)	26(3.9)	37(5.5)	23(3.5)	0.076
MUSCULO-SKELETAL SYSTEM DISORDERS	38(5.5)	31(4.5)	33(5.0)	34(5.1)	20(3.0)	0.088
ARTHRALGIA	15 (2.2)	12 (1.7)	7 (1.1)	6 (0.9)	7 (1.1)	0.030
MYO ENDO PERICARDIAL & VALVE DISORDERS	5(0.7)	1(0.1)	5(0.8)	7(1.0)	2(0.3)	0.941
NEOPLASM	3(0.4)	3(0.4)	5(0.8)	2(0.3)	2(0.3)	0.627
PLATELET, BLEEDING & CLOTTING DISORDERS	8(1.2)	7(1.0)	8(1.2)	6(0.9)	12(1.8)	0.377
PSYCHIATRICDISORDERS	43 (6.3)	35 (5.1)	42 (6.3)	41 (6.1)	38 (5.8)	0.975
RED BLOOD CELL DISORDERS	1 (0.1)	3 (0.4)	3 (0.5)	4 (0.6)	4 (0.6)	0.178
REPRODUCTIVE DISORDERS, FEMALE	5 (0.7)	8 (1.2)	8 (1.2)	5 (0.7)	9 (1.4)	0.485
REPRODUCTIVE DISORDERS, MALE	2 (0.3)	1 (0.1)	1 (0.2)	2 (0.3)	0 (0.0)	0.408
RESISTANCE MECHANISM DISORDERS	9 (1.3)	18 (2.6)	19 (2.9)	15 (2.2)	14 (2.1)	0.470
RESPIRATORY SYSTEM DISORDERS	120 (17.5)	136 (19.7)	145 (21.8)	137 (20.4)	133 (20.3)	0.194
SKIN AND APPENDAGES DISORDERS	49 (7.2)	46 (6.6)	31 (4.7)	35 (5.2)	33 (5.0)	0.044
RASH	21(3.1)	15(2.2)	13(2.0)	8(1.2)	10(1.5)	0.017
SPECIAL SENSES OTHER, DISORDERS	0 (0.0)	2 (0.3)	2 (0.3)	1 (0.1)	0 (0.0)	0.779
URINARY SYSTEM DISORDERS	19 (2.8)	20 (2.9)	26 (3.9)	24 (3.6)	20 (3.0)	0.557
MICTURITION FREQUENCY	0 (0.0)	3 (0.4)	7 (1.1)	5 (0.7)	5 (0.8)	0.048
VASCULAR (EXTRACARDIAC) DISORDERS	3 (0.4)	3 (0.4)	6 (0.9)	3 (0.4)	3 (0.5)	0.944
VISIONDISORDERS	9 (1.3)	13 (1.9)	11 (1.7)	8 (1.2)	9 (1.4)	0.698
WHITECELLANDRESDISORDERS	5 (0.7)	2 (0.3)	2 (0.3)	0 (0.0)	3 (0.5)	0.242

* p values were from the Mantel-Haenszel chi-square test

Table 4.2 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Autonomic nervous system, Gastro-intestinal system. Within "central and peripheral nervous system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): cramped legs. Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): Abdominal pain, constipation, dyspepsia, flatulence, nausea, vomiting. Within "respiratory system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): coughing. Within "skin and appendages", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): rash.

Table 4.2 Number of Subjects Reporting Treatment-Related Adverse Events (12 week studies)

	Placebo N=685	50mg BID N=692	100mg BID N=664	200mg BID N=672	Naproxan N=656	P-Value*
Body System	N (%)	N (%)	N (%)	N (%)	N (%)	
APPLICATION SITE DISORDERS	0(0.0)	2(0.3)	4(0.6)	3(0.4)	1(0.2)	0.469
AUTONOMIC NERVOUS SYSTEM DISORDERS	5(0.7)	3(0.4)	7(1.1)	12(1.8)	10(1.5)	0.020
BODY AS A WHOLE-GENERAL DISORDERS	35(5.1)	52(7.5)	56(8.4)	59(8.8)	45(6.9)	0.126
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	0(0.0)	0(0.0)	1(0.1)	1(0.2)	0.661
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	93(13.6)	75(10.8)	99(14.9)	85(12.6)	68(10.4)	0.264
CRAMPS LEGS	1(0.1)	2(0.3)	1(0.2)	7(1.0)	6(0.9)	0.008
ENDOCRINE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.306
GASTRO-INTESTINAL SYSTEM DISORDERS	109(15.9)	121(17.5)	135(20.3)	144(21.4)	171(26.1)	<.001
ABDOMINAL PAIN	16(2.3)	24(3.5)	26(3.9)	28(4.2)	33(5.0)	0.009
CONSTIPATION	8(1.2)	7(1.0)	10(1.5)	10(1.5)	24(3.7)	0.001
DYSPEPSIA	41(6.0)	44(6.4)	44(6.6)	54(8.0)	65(9.9)	0.003
FLATULENCE	7(1.0)	14(2.0)	10(1.5)	9(1.3)	20(3.0)	0.039
NAUSEA	21(3.1)	19(2.7)	20(3.0)	26(3.9)	31(4.7)	0.048
VOMITING	1(0.1)	4(0.6)	7(1.1)	9(1.3)	6(0.9)	0.033
HEARING AND VESTIBULAR DISORDERS	3(0.4)	3(0.4)	4(0.6)	3(0.4)	2(0.3)	0.762
HEARTRATE AND RHYTHM DISORDERS	1(0.1)	3(0.4)	2(0.3)	6(0.9)	5(0.8)	0.050
LIVER AND BILIARY SYSTEM DISORDERS	5(0.7)	5(0.7)	4(0.6)	5(0.7)	5(0.8)	0.936
METABOLIC AND NUTRITIONAL DISORDERS	12(1.8)	18(2.6)	16(2.4)	27(4.0)	15(2.3)	0.193
MUSCULO-SKELETAL SYSTEM DISORDERS	15(2.2)	12(1.7)	16(2.4)	14(2.1)	6(0.9)	0.191
MYO ENDO PERICARDIAL & VALVE DISORDERS	3(0.4)	1(0.1)	3(0.5)	3(0.4)	1(0.2)	0.709
NEOPLASM	3(0.4)	2(0.3)	1(0.2)	1(0.1)	0(0.0)	0.067
PLATELET, BLEEDING & CLOTTING DISORDERS	6(0.9)	4(0.6)	5(0.8)	4(0.6)	7(1.1)	0.717
PSYCHIATRIC DISORDERS	27(3.9)	23(3.3)	31(4.7)	29(4.3)	24(3.7)	0.847
RED BLOOD CELL DISORDERS	1(0.1)	2(0.3)	2(0.3)	3(0.4)	4(0.6)	0.136
REPRODUCTIVE DISORDERS, FEMALE	3(0.4)	3(0.4)	6(0.9)	4(0.6)	3(0.5)	0.815
REPRODUCTIVE DISORDERS, MALE	0(0.0)	1(0.1)	0(0.0)	1(0.1)	0(0.0)	0.982
RESISTANCE MECHANISM DISORDERS	4(0.6)	8(1.2)	4(0.6)	5(0.7)	7(1.1)	0.624
RESPIRATORY SYSTEM DISORDERS	29(4.2)	41(5.9)	43(6.5)	43(6.4)	29(4.4)	0.737
COUGHING	1(0.1)	4(0.6)	3(0.5)	3(0.4)	8(1.2)	0.029
SKIN AND APPENDAGES DISORDERS	35(5.1)	32(4.6)	20(3.0)	27(4.0)	23(3.5)	0.111
RASH	17(2.5)	12(1.7)	9(1.4)	8(1.2)	7(1.1)	0.026
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	2(0.3)	2(0.3)	0(0.0)	0(0.0)	0.500
URINARY SYSTEM DISORDERS	10(1.5)	8(1.2)	15(2.3)	10(1.5)	8(1.2)	0.935
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	1(0.1)	2(0.3)	1(0.1)	2(0.3)	0.563
VISION DISORDERS	4(0.6)	9(1.3)	7(1.1)	4(0.6)	4(0.6)	0.559
WHITE CELL AND RES DISORDERS	3(0.4)	0(0.0)	2(0.3)	0(0.0)	1(0.2)	0.264

*p values were from the Mantel-Haenszel chi-square test

Table 4.3 lists the frequencies of all reported severe adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: platelet, bleeding and clotting system, reproductive system (female). Within "Gastro-intestinal system", the frequencies of the following adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test): dyspepsia.

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Table 4.3 Number of Subjects Reporting All-Causalities Severe Adverse Events (12 week studies)

	Placebo N=685	50mgBID N=692	100mgBID N=664	200mgBID N=672	Naproxan N=656	P-Value*
Body System	N(%)	N(%)	N(%)	N(%)	N(%)	
APPLICATIONSITEDISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487
AUTONOMIC NERVOUS SYSTEM DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.3)	1(0.2)	0.095
BODY AS A WHOLE-GENERAL DISORDERS	8(1.2)	10(1.4)	9(1.4)	16(2.4)	5(0.8)	0.909
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0.974
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	17(2.5)	17(2.5)	16(2.4)	14(2.1)	15(2.3)	0.677
GASTRO-INTESTINAL SYSTEM DISORDERS	16(2.3)	15(2.2)	16(2.4)	12(1.8)	23(3.5)	0.308
DYSPEPSIA	1(0.1)	5(0.7)	4(0.6)	5(0.7)	8(1.2)	0.031
HEART RATE AND RHYTHM DISORDERS	1(0.1)	1(0.1)	1(0.2)	0(0.0)	1(0.2)	0.748
LIVER AND BILIARY SYSTEM DISORDERS	2(0.3)	0(0.0)	1(0.2)	0(0.0)	2(0.3)	0.971
METABOLIC AND NUTRITIONAL DISORDERS	0(0.0)	1(0.1)	1(0.2)	0(0.0)	0(0.0)	0.633
MUSCULO-SKELETAL SYSTEM DISORDERS	6(0.9)	4(0.6)	3(0.5)	7(1.0)	1(0.2)	0.313
MYO ENDO PERICARDIAL & VALVE DISORDERS	3(0.4)	0(0.0)	0(0.0)	4(0.6)	0(0.0)	0.621
NEOPLASM	1(0.1)	1(0.1)	1(0.2)	0(0.0)	2(0.3)	0.724
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	0(0.0)	0(0.0)	1(0.1)	3(0.5)	0.012
PSYCHIATRIC DISORDERS	3(0.4)	1(0.1)	3(0.5)	1(0.1)	1(0.2)	0.370
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	1(0.2)	0(0.0)	3(0.5)	0.031
RESISTANCE MECHANISM DISORDERS	2(0.3)	0(0.0)	2(0.3)	1(0.1)	1(0.2)	0.803
RESPIRATORY SYSTEM DISORDERS	6(0.9)	7(1.0)	2(0.3)	5(0.7)	5(0.8)	0.627
SKIN AND APPENDAGES DISORDERS	3(0.4)	5(0.7)	3(0.5)	1(0.1)	2(0.3)	0.282
URINARY SYSTEM DISORDERS	0(0.0)	1(0.1)	2(0.3)	0(0.0)	0(0.0)	0.704
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.160
VISION DISORDERS	0(0.0)	0(0.0)	2(0.3)	0(0.0)	0(0.0)	0.982
WHITE CELL AND RES DISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487

*p values were from the Mantel-Haenszel chi-square test

Table 4.4 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) severe adverse events in the 12-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: platelet, bleeding and clotting system.

Table 4.4 Number of Subjects Reporting Treatment-Related severe Adverse Events (12 week studies)

	Placebo N=685	50mgBID N=692	100mgBID N=664	200mgBID N=672	Naproxan N=656	P-Value*
Body System	N(%)	N(%)	N(%)	N(%)	N(%)	
AUTONOMIC NERVOUS SYSTEM DISORDERS	0(0.0)	0(0.0)	0(0.0)	2(0.3)	1(0.2)	0.095
BODY AS A WHOLE-GENERAL DISORDERS	2(0.3)	5(0.7)	3(0.5)	7(1.0)	0(0.0)	0.782
CARDIOVASCULAR DISORDERS, GENERAL	1(0.1)	0(0.0)	0(0.0)	0(0.0)	1(0.2)	0.982
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	8(1.2)	7(1.0)	10(1.5)	5(0.7)	6(0.9)	0.540
GASTRO-INTESTINAL SYSTEM DISORDERS	7(1.0)	13(1.9)	13(2.0)	8(1.2)	18(2.7)	0.088
METABOLIC AND NUTRITIONAL DISORDERS	0(0.0)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.487
MUSCULO-SKELETAL SYSTEM DISORDERS	4(0.6)	1(0.1)	1(0.2)	3(0.4)	0(0.0)	0.171
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.1)	0(0.0)	0(0.0)	1(0.1)	0(0.0)	0.632
NEOPLASM	1(0.1)	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0.138
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(0.3)	0.042
PSYCHIATRIC DISORDERS	2(0.3)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.500
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	1(0.2)	0(0.0)	1(0.2)	0.306
RESISTANCE MECHANISM DISORDERS	1(0.1)	0(0.0)	1(0.2)	1(0.1)	1(0.2)	0.699
RESPIRATORY SYSTEM DISORDERS	2(0.3)	1(0.1)	0(0.0)	1(0.1)	1(0.2)	0.549
SKIN AND APPENDAGES DISORDERS	2(0.3)	5(0.7)	2(0.3)	1(0.1)	2(0.3)	0.446
URINARY SYSTEM DISORDERS	0(0.0)	0(0.0)	1(0.2)	0(0.0)	0(0.0)	0.987
VASCULAR (EXTRACARDIAC) DISORDERS	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0.160

*p values were from the Mantel-Haenszel chi-square test

Reviewer's comments :

In the three 12-week studies, the frequencies of reported adverse events by body system in the treatment groups were statistically significant (Table 4.1) in the Gastro-intestinal system ($p<0.001$, with naproxan group having the highest frequency), skin and appendages. ($p=0.044$, Placebo group had the highest frequency) and the respiratory system ($p=0.024$, the two SC-58635 groups had the highest frequency). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.1): Dema Peripheral ($p=0.026$, SC-58635 200 mg bid group had the highest frequency), allergic reaction ($p=0.048$, SC-58635 200 mg bid group had the highest frequency), and chest pain ($p=0.016$, the naproxan group had the highest frequency), headache ($p=0.003$, placebo group had the highest frequency), Abdominal pain ($p=0.014$, the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), constipation ($p<0.001$, the naproxan group had the highest frequency), dyspepsia ($p=0.002$ the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), flatulence ($p=0.018$, the naproxan group had the highest frequency), vomiting ($p=0.049$, the SC-58635 100 and 200 mg bid groups and the naproxan group had higher frequencies), arthralgia ($p=0.030$, the placebo group had highest frequency), rash ($p=0.017$, the placebo group had the highest frequency), micturition frequency($p=0.048$, the placebo group had lowest frequency).

The frequencies of reported treatment-related adverse events by body system in the treatment groups were statistically significant (Table 4.2) in the autonomic nervous system ($p=0.020$, with the SC-58635 200 mg bid group and the naproxan group having the highest frequencies), the Gastro-intestinal system ($p<0.001$, with naproxan group having the highest frequency), heart and rhythm system ($p=0.05$, with the SC-58635 200 mg bid group and the naproxan group having the highest frequencies). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.2): Leg cramps ($p=0.008$, the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), abdominal pain ($p=0.009$, the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), constipation ($p=0.001$, the naproxan group had the highest frequency), dyspepsia ($p=0.003$, the SC-58635 200 mg bid group and the naproxan group had the highest frequencies), flatulence ($p=0.039$, the naproxan group had the highest frequency), nausea ($p=0.048$, the naproxan group had the highest frequency), vomiting ($p=0.033$, the SC-58635 100 and 200 mg bid groups and the naproxan group had higher frequencies), coughing ($p=0.029$, the naproxan group had highest frequency), rash ($p=0.026$, the placebo group had the highest frequency).

The frequencies of reported severe adverse events by body system in the treatment groups were statistically significant (Table 4.3) in the platelet, bleeding and clotting system ($p=0.020$, the SC-58635 200 mg bid group and the naproxan group had higher frequencies), female reproductive system ($p=0.031$, the naproxan group had the highest frequency). The frequencies of the following reported adverse events (by individual events) in the treatment groups were statistically significant (Table 4.3): dyspepsia ($p=0.031$, the naproxan group had the highest frequency).

The frequencies of reported severe treatment-related adverse events by body system in the treatment groups were statistically significant (Table 4.4) in the platelet, bleeding and clotting system ($p=0.042$, the naproxan group being the only group with this event).

6 week studies:

Table 4.5 lists the frequencies of all reported adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Musculo-skeletol system, respiratory system.

Table 4.5 Number of Subjects Reporting All-Causalities Adverse Events (6 week studies)

Body System	Placebo N=476	100mg BID N=474	200mg QD N=454	P-Value*
	N (%)	N (%)	N (%)	
APPLICATION SITE DISORDERS	0(0.0)	3(0.6)	1(0.2)	0.513
AUTONOMIC NERVOUS SYSTEM DISORDERS	7(1.5)	8(1.7)	8(1.8)	0.725
BODY AS A WHOLE-GENERAL DISORDERS	60(12.6)	61(12.9)	48(10.6)	0.346
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	2(0.4)	0(0.0)	0.998
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	103(21.6)	88(18.6)	96(21.1)	0.839
ENDOCRINE DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
GASTRO-INTESTINAL SYSTEM DISORDERS	66(13.9)	89(18.8)	71(15.6)	0.446
HEARING AND VESTIBULAR DISORDERS	4(0.8)	5(1.1)	3(0.7)	0.772
HEART RATE AND RHYTHM DISORDERS	1(0.2)	2(0.4)	1(0.2)	0.969
LIVER AND BILIARY SYSTEM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
METABOLIC AND NUTRITIONAL DISORDERS	8(1.7)	7(1.5)	9(2.0)	0.728
MUSCULO-SKELETAL SYSTEM DISORDERS	23(4.8)	15(3.2)	11(2.4)	0.045
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978
NEOPLASM	1(0.2)	1(0.2)	0(0.0)	0.388
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
PSYCHIATRIC DISORDERS	20(4.2)	16(3.4)	14(3.1)	0.356
RED BLOOD CELL DISORDERS	0(0.0)	1(0.2)	2(0.4)	0.146
REPRODUCTIVE DISORDERS, FEMALE	4(0.8)	2(0.4)	6(1.3)	0.436
REPRODUCTIVE DISORDERS, MALE	1(0.2)	0(0.0)	1(0.2)	0.978
RESISTANCE MECHANISM DISORDERS	5(1.1)	10(2.1)	6(1.3)	0.720
RESPIRATORY SYSTEM DISORDERS	39(8.2)	55(11.6)	58(12.8)	0.024
SKIN AND APPENDAGES DISORDERS	26(5.5)	17(3.6)	15(3.3)	0.096
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
URINARY SYSTEM DISORDERS	9(1.9)	6(1.3)	4(0.9)	0.182
VASCULAR (EXTRACARDIAC) DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
VISION DISORDERS	6(1.3)	4(0.8)	8(1.8)	0.506
WHITE CELL AND RES DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978

* p values were from the Mantel-Haenszel chi-square test

Table 4.6 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were statistically significantly different ($p \leq 0.05$ by the Mantel-Haenszel chi-square test) in the following body systems: Musculo-skeletol system.

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Table 4.6 Number of Subjects Reporting Treatment-Related Adverse Events (6 week studies)

Body System	Placebo N=476	100mg BID N=474	200mg QD N=454	P-Value*
	N (%)	N (%)	N (%)	
APPLICATION SITE DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
AUTONOMIC NERVOUS SYSTEM DISORDERS	5(1.1)	3(0.6)	5(1.1)	0.944
BODY AS A WHOLE-GENERAL DISORDERS	15(3.2)	16(3.4)	10(2.2)	0.396
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	37(7.8)	32(6.8)	40(8.8)	0.564
GASTRO-INTESTINAL SYSTEM DISORDERS	46(9.7)	56(11.8)	47(10.4)	0.723
HEARING AND VESTIBULAR DISORDERS	1(0.2)	1(0.2)	2(0.4)	0.513
HEART RATE AND RHYTHM DISORDERS	1(0.2)	2(0.4)	1(0.2)	0.969
LIVER AND BILIARY SYSTEM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
METABOLIC AND NUTRITIONAL DISORDERS	5(1.1)	5(1.1)	7(1.5)	0.497
MUSCULO-SKELETAL SYSTEM DISORDERS	6(1.3)	4(0.8)	0(0.0)	0.020
MYO ENDO PERICARDIAL & VALVE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0.212
PLATELET, BLEEDING & CLOTTING DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
PSYCHIATRIC DISORDERS	10(2.1)	7(1.5)	7(1.5)	0.507
RED BLOOD CELL DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
REPRODUCTIVE DISORDERS, MALE	0(0.0)	0(0.0)	1(0.2)	0.212
RESISTANCE MECHANISM DISORDERS	0(0.0)	1(0.2)	1(0.2)	0.370
RESPIRATORY SYSTEM DISORDERS	4(0.8)	7(1.5)	7(1.5)	0.339
SKIN AND APPENDAGES DISORDERS	18(3.8)	6(1.3)	10(2.2)	0.111
SPECIAL SENSES OTHER, DISORDERS	0(0.0)	0(0.0)	2(0.4)	0.077
URINARY SYSTEM DISORDERS	2(0.4)	1(0.2)	0(0.0)	0.158
VASCULAR (EXTRACARDIAC) DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
VISION DISORDERS	4(0.8)	0(0.0)	5(1.1)	0.639

*p values were from the Mantel-Haenszel chi-square test

Table 4.7 lists the frequencies of all reported severe adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were not statistically significantly different ($p \geq 0.05$ by the Mantel-Haenszel chi-square test) in all the body systems.

Table 4.7 Number of Subjects Reporting All-Causalities Severe Adverse Events (6 week studies)

Body System	Placebo N=476	100mg BID N=474	200mg QD N=454	P-Value*
	N (%)	N (%)	N (%)	
AUTONOMIC NERVOUS SYSTEM DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
BODY AS A WHOLE-GENERAL DISORDERS	9(1.9)	3(0.6)	5(1.1)	0.263
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	5(1.1)	8(1.7)	8(1.8)	0.369
GASTRO-INTESTINAL SYSTEM DISORDERS	7(1.5)	9(1.9)	5(1.1)	0.652
METABOLIC AND NUTRITIONAL DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
MUSCULO-SKELETAL SYSTEM DISORDERS	3(0.6)	1(0.2)	0(0.0)	0.067
MYO ENDO PERICARDIAL & VALVE DISORDERS	1(0.2)	0(0.0)	1(0.2)	0.978
NEOPLASM	1(0.2)	0(0.0)	0(0.0)	0.221
PSYCHIATRIC DISORDERS	1(0.2)	1(0.2)	0(0.0)	0.388
REPRODUCTIVE DISORDERS, FEMALE	0(0.0)	0(0.0)	2(0.4)	0.077
RESISTANCE MECHANISM DISORDERS	0(0.0)	3(0.6)	0(0.0)	0.998
RESPIRATORY SYSTEM DISORDERS	0(0.0)	2(0.4)	1(0.2)	0.457
SKIN AND APPENDAGES DISORDERS	5(1.1)	1(0.2)	1(0.2)	0.070
URINARY SYSTEM DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221

*p values were from the Mantel-Haenszel chi-square test

Table 4.8 lists the frequencies of all reported treatment related (relationship with treatment coded as "uncertain" or "probable" by the investigators) severe adverse events in the 6-week studies. The frequencies of the adverse events in the treatment groups were not statistically significantly different ($p > 0.05$ by the Mantel-Haenszel chi-square test) in all the body systems.

Table 4.8 Number of Subjects Reporting Treatment-Related severe Adverse Events (6 week studies)

Body System	Placebo	100mg BID	200mg QD	P-Value*
	N=476	N=474	N=454	
AUTONOMIC NERVOUS SYSTEM DISORDERS	2(0.4)	0(0.0)	0(0.0)	0.084
BODY AS A WHOLE-GENERAL DISORDERS	3(0.6)	1(0.2)	0(0.0)	0.067
CARDIOVASCULAR DISORDERS, GENERAL	0(0.0)	1(0.2)	0(0.0)	0.999
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	4(0.8)	3(0.6)	3(0.7)	0.742
GASTRO-INTESTINAL SYSTEM DISORDERS	6(1.3)	5(1.1)	2(0.4)	0.194
METABOLIC AND NUTRITIONAL DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221
MUSCULO-SKELETAL SYSTEM DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221
MYO ENDO PERICARDIAL & VALVE DISORDERS	0(0.0)	0(0.0)	1(0.2)	0.212
PSYCHIATRIC DISORDERS	1(0.2)	0(0.0)	0(0.0)	0.221
RESPIRATORY SYSTEM DISORDERS	0(0.0)	1(0.2)	0(0.0)	0.999
SKIN AND APPENDAGES DISORDERS	3(0.6)	0(0.0)	1(0.2)	0.233

* p values were from the Mantel-Haenszel chi-square test

Reviewer's comments : In the two 6-week studies, the frequencies of reported adverse events by body system in the treatment groups were statistically significant (Table 4.5) in the musculo-skeletal system ($p=0.045$, Placebo group had the highest frequency) and the respiratory system ($p=0.024$, the two SC-58635 groups had higher frequencies). The frequencies of reported treatment related adverse events by body system in the treatment groups were statistically significant (Table 4.6) in the musculo-skeletal system ($p=0.020$, Placebo group had the highest frequency). The frequencies of all other reported adverse events, reported treatment-related adverse events, reported severe adverse events, reported treatment-related severe adverse events for the treatment groups were not statistically significant.

Reviewer's Summary and Conclusion (which may be conveyed to the sponsor):

Efficacy Results:

In Studies N49-96-02-020, N49-96-02-021 and N49-98-06-054, the SC-58635 100 mg BID, and SC-58635 200 mg BID groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, SC-58635 200 mg BID groups, and the naproxen group. These results were supported by the analyses of the secondary and the supportive variables.

In Studies N49-98-06-060 and N49-98-02-087, the SC-58635 100 mg BID, and SC-58635 200 mg QD groups were demonstrated to be statistically superior to the placebo group in the treatment of OA of the knee, in terms of the primary efficacy variables. There were no statistically significant differences between the SC-58635 100 mg BID, and SC-58635 200 mg QD groups. These results were supported by the analyses of the secondary and the supportive variables.

Gastro-intestinal results:

In study N49-96-02-021, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with all other treatment groups ($p \leq 0.05$). There was no difference in the incidence of ulcers in the placebo group compared with any of the SC-58635 groups ($p>0.05$) or in the incidence of ulcers among the SC-58635 groups ($p \geq 0.05$).

In study N49-97-02-062, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group were significantly greater compared with the SC-58635 group ($p \leq 0.05$).

In study N49- 97- 02- 071, the incidence of ulceration (gastroduodenal, gastric, duodenal) in the naproxen group to be significantly greater compared with the SC-58635 group and the diclofenac group ($p \leq 0.05$). There was no difference in the incidence of gastroduodenal and gastric ulcers in the SC-58635 group and the diclofenac group ($p > 0.05$). The incidence of duodenal ulcers in the diclofenac group was significantly greater compared with the SC-58635 group ($p \leq 0.05$).

Conclusion:

The sponsor demonstrated that the SC-58635 100 mg BID, 200 bid, 200 mg QD groups were statistically superior to the placebo group in the treatment of OA of the knee, or the hip. The SC-58635 groups had lower incidence of ulceration (gastroduodenal, gastric, duodenal) than the naproxen group. In general, the frequency of reported adverse events for the SC-58635 groups were lower than the naproxen group.

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HFD-550/Dr. Hyde
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HFD-725/Dr. Gao
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Appendix: Tables

A.1 Statistical analyses for study N49-96-02-020

Table A.1 Patient disposition- N49-96-02-020

	Placebo	SC-58635 50mg BID	SC-58635 100mg BID	SC-58635 200mg BID	NAPROXEN 500mg BID	Total
Randomized	204	203	197	202	198	1004
Week 2	171	178	179	187	184	899
Week 6	115	146	132	150	142	685
Week 12	91	118	116	129	116	570
ITT	203	203	197	202	198	1003

A.1.1 Primary variables- primary analyses

Table A.2 Primary variable: Patients global assessment of Arthritis
mean change from baseline--study N49-96-02-020

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	203	-0.61895207	-0.67900843	-0.63917919
50. mg	203	-0.90561260	-0.87891660	-0.91815870
100 mg	197	-1.17165707	-1.19406587	-1.15334698
200 mg	202	-1.13214075	-1.12947462	-1.08819098
Naproxen (NP)	198	-1.07153909	-1.08962113	-0.95467074
Contrast				
100mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.6469	p=0.4880	p=0.4972
100mg vs. NP		p=0.2482	p=0.2645	p=0.0395
200mg vs. NP		p=0.4819	p=0.6684	p=0.1638

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**Table A.3 Primary variable: Physician's global assessment of Arthritis
mean change from baseline--study N49-96-02-020**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	203	-0.58588367	-0.68200648	-0.66317528
50 mg	203	-0.88053921	-0.92895679	-0.92367101
100 mg	197	-1.151572312	-1.15154308	-1.13488857
200 mg	202	-1.06804926	-1.10181045	-1.01661487
Naproxen (NP)	198	-1.05470934	-1.09601711	-1.01241875
Contrast				
100mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001	p= 0.0001
100mg vs. 200mg		p= 0.2969	p= 0.5730	p= 0.2003
100mg vs. NP		p= 0.2289	p= 0.5313	p= 0.1870
200mg vs. NP		p= 0.8678	p= 0.9476	p= 0.9637

**Table A.4 Primary variable: Patients' assessment of Pain (VAS)
mean change from baseline--study N49-96-02-020**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	201	-12.1062014	-16.6474573	-15.0586010
50 mg	203	-18.3721644	-17.9189424	-15.9747610
100 mg	196	-26.1486246	-25.9293698	-23.1436807
200 mg	201	-24.5744804	-24.4642813	-22.0998937
Naproxen (NP)	197	-27.2728161	-26.9555508	-22.7110434
Contrast				
100mg vs. PL		p= 0.0001	p= 0.0005	p= 0.0031
200mg vs. PL		p= 0.0001	p= 0.0030	p= 0.0094
100mg vs. 200mg		p=0.5139	p=0.5793	p=0.7015
100mg vs. NP		p=0.6432	p=0.6997	p=0.8746
200mg vs. NP		p=0.2632	p=0.3459	p=0.8224

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**Table A.5 Primary variable: Womac composite score
mean change from baseline--study N49-96-02-020**

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	182	-3.5685252	-5.5530410
50 mg	174	-9.6524175	-9.6284772
100 mg	175	-13.4348877	-13.6402678
200 mg	181	-12.5459744	-12.0828427
Naproxen (NP)	177	-11.8750061	-11.3339654
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.5486	p=0.3544
100mg vs. NP		p=0.2960	p=0.1734
200mg vs. NP		p=0.6500	p=0.6554

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**Table A.6 Primary variable: Womac pain score
mean change from baseline--study N49-96-02-020**

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	201	-0.70188403	-1.22582027
50 mg	197	-1.97598478	-2.01497020
100 mg	196	-3.00114460	-3.11755073
200 mg	201	-2.79725690	-2.71633237
Naproxen (NP)	198	-2.69704223	-2.37705744
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.5205	p=0.2592
100mg vs. NP		p=0.3398	p=0.0382
200mg vs. NP		p=0.7514	p=0.3387

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**Table A.7 Primary variable: Womac joint stiffness
mean change from baseline--study N49-96-02-020**

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	202	-0.32961202	-0.52364706
50 mg	197	-0.89110028	-0.89737084
100 mg	196	-1.23084194	-1.23065992
200 mg	201	-1.20807264	-1.11553949
Naproxen (NP)	195	-1.13532232	-1.11453603
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0001
100mg vs. 200mg		p=0.8741	p=0.4467
100mg vs. NP		p=0.5097	p=0.4465
200mg vs. NP		p=0.6127	p=0.9947

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Table A.8 Primary variable: Womac physical functions
mean change from baseline--study N49-96-02-020

		Change from Baseline (least square mean)	
Treatment	N	week 2	week 12
Placebo (PL)	184	-2.58857972	-3.93638477
50 mg	174	-6.79507377	-6.83882973
100 mg	176	-9.31779900	-9.47018393
200 mg	181	-8.51862356	-8.10791944
Naproxen (NP)	180	-8.02677075	-7.79015304
Contrast			
100mg vs. PL		p= 0.0001	p= 0.0001
200mg vs. PL		p= 0.0001	p= 0.0006
100mg vs. 200mg		p=0.4595	p=0.2645
100mg vs. NP		p=0.2331	p=0.1697
200mg vs. NP		p=0.6472	p=0.7935

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Table A.9 Primary variable: Patients global assessment of Arthritis
categorical change from baseline--study N49-96-02-020

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	203	36 (17.7%)	153 (75.4%)	14 (6.9%)	45 (22.2%)	141 (69.5%)	17 (8.4%)	49 (24.1%)	135 (66.5%)	19 (9.4%)
50 mg	203	49 (24.1%)	152 (74.9%)	2 (1%)	55 (27.1%)	144 (70.9%)	4 (2.0%)	54 (26.6%)	147 (72.4%)	2 (1%)
100 mg	197	72 (36.6%)	124 (62.9%)	1 (0.5%)	80 (40.6%)	115 (58.4%)	2 (1.0%)	69 (35%)	126 (64%)	2 (1%)
200 mg	202	70 (34.7%)	132 (65.4%)	0 (0%)	75 (37.1%)	126 (62.4%)	1 (0.5%)	72 (35.6%)	128 (63.4%)	2 (1%)
Naproxen (NP)	198	65 (32.8%)	131 (66.2%)	2 (1%)	66 (33.3%)	129 (65.2%)	3 (1.5%)	58 (29.3%)	137 (69.2%)	3 (1.5%)
pairwise comparison										
100mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
200mg vs. PL		p= 0.001			p= 0.001			p= 0.001		
100mg vs. 200mg		p=0.745			p=0.523			p=0.897		
100mg vs. NP		p=0.405			p=0.127			p=0.208		
200mg vs. NP		p=0.601			p=0.360			p=0.163		

*Imp=Improved, Nchg=No change, Wors=worsened

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Table A.10 Primary variable: Physician's global assessment of Arthritis
categorical change from baseline--study N49-96-02-020

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	203	29 (14.3%)	168 (82.8%)	6 (3%)	44 (21.7%)	152 (74.9%)	7 (3.5%)	42 (20.7%)	152 (74.9%)	9 (4.4%)
50 mg	203	51 (25.1%)	148 (72.9%)	4 (2%)	64 (31.5%)	135 (66.5%)	4 (2%)	60 (29.6%)	139 (68.5%)	4 (2%)
100 mg	197	68 (34.5%)	128 (65%)	1 (0.5%)	72 (36.6%)	122 (61.9%)	3 (1.5%)	71 (36%)	123 (62.4%)	3 (1.5%)
200 mg	202	54 (26.7%)	147 (72.8%)	1 (0.5%)	65 (32.2%)	136 (67.3%)	1 (0.5%)	64 (31.7%)	137 (67.8%)	1 (0.5%)
Naproxen (NP)	198	65 (32.8%)	131 (66.2%)	2 (1%)	70 (35.4%)	126 (63.6%)	2 (1%)	65 (32.8%)	131 (66.2%)	2 (1%)
pairwise comparison										
100mg vs. PL		p= 0.001				p= 0.001				p= 0.001
200mg vs. PL		p= 0.001				p= 0.006				p= 0.003
100mg vs. 200mg		p=0.096				p=0.447				p=0.448
100mg vs. NP		p=0.675				p=0.862				p=0.558
200mg vs. NP		p=0.218				p=0.556				p=0.867

*Imp=Improved, Nchg=No change, Wors=worsened

A.1.2 Secondary Variables

Table A.11 Secondary variable: Patients' withdrawal due to lack of efficacy
study N49-96-02-020

	withdrawal due to lack of efficacy		pairwise comparison
	Yes	No	
Treatment	N (%)	N (%)	
Placebo (PL)	79 (38.9%)	124 (61.1%)	100mg vs. PL: p= 0.001 200mg vs. PL : p= 0.002
50 mg	61 (30.05%)	142 (69.95%)	100mg vs. 200mg: p=0.344
100 mg	40 (20.3%)	157 (79.7%)	100mg vs. NP: p=0.162
200 mg	49 (24.3%)	153 (75.7%)	200mg vs. NP: p=0.645
Naproxen (NP)	52 (26.3%)	146 (73.7%)	

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Table A.12 Secondary variable: Time to withdrawal due to lack of efficacy
study N49-96-02-020

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	79 (38.9%)	51.48 (1.99)	100mg vs. PL: p= 0.0001 200mg vs. PL : p= 0.0002
50 mg	61 (30.05%)	57.12 (1.64)	100mg vs. 200mg: p=0.0647
100 mg	40 (20.3%)	57.88 (1.40)	100mg vs. NP: p=0.2948
200 mg	49 (24.3%)	68.84 (1.80)	200mg vs. NP: p=0.5297
Naproxen (NP)	52 (26.3%)	57.03 (1.54)	

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**Table A.13 Secondary variable: APS Pain scale—Total score
study N49-96-02-020**

Treatment	N	day 1	day 2	day3	day4	day5	day 6	day 7
Placebo (PL)	144	-1.84	-3.25	-4.40	-4.98	-5.66	-5.60	-6.26
50 mg	142	-2.73	-5.66	-6.62	-6.89	-7.38	-7.51	-7.99
100 mg	143	-3.43	-7.53	-8.11	-9.45	-10.69	-11.62	-11.61
200 mg	142	-3.08	-6.14	-8.08	-9.30	-10.16	-11.45	-11.71
Naproxen (NP)	144	-4.63	-8.88	-10.17	-10.91	-11.70	-12.25	-11.75
Contrast								
100mg vs. PL: p=	0.1892	0.0015	0.0115	0.0028	0.0011	0.0002	0.0011	
200mg vs. PL : p=	0.3063	0.0319	0.0122	0.0040	0.0034	0.0002	0.0009	
100mg vs. 200mg: p=	0.7722	0.2995	0.9846	0.9172	0.7328	0.9123	0.9526	
100mg vs. NP: p=	0.3176	0.3154	0.1583	0.3280	0.5052	0.6921	0.9305	
200mg vs. NP: p=	0.1987	0.0417	0.1542	0.2808	0.3147	0.6138	0.9782	

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A.1.3 Supportive variables:

**Table A.14 Supportive variable: Functional capacity classification
mean change from baseline--study N49-96-02-020**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	203	-0.096	-0.135	-0.125
50 mg	203	-0.153	-0.156	-0.134
100 mg	197	-0.232	-0.203	-0.220
200 mg	202	-0.192	-0.227	-0.214
Naproxen (NP)	198	-0.210	-0.196	-0.167
Contrast				
100mg vs. PL: p=	0.0004	0.1017	0.0335	
200mg vs. PL : p=	0.0115	0.0264	0.0461	
100mg vs. 200mg: p=	0.2927	0.5676	0.8853	
100mg vs. NP: p=	0.5750	0.8664	0.2349	
200mg vs. NP: p=	0.6241	0.4583	0.2936	

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**Table A.15 Supportive variable: Osteoarthritis severity index
mean change from baseline--study N49-96-02-020**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	203	-1.529	-1.841	-1.928
50 mg	203	-3.063	-3.201	-3.212
100 mg	197	-3.460	-3.845	-3.754
200 mg	202	-3.482	-3.656	-3.346
Naproxen (NP)	198	-3.427	-3.539	-2.958
Contrast				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0003
100mg vs. 200mg: p=		0.9502	0.6343	0.3044
100mg vs. NP: p=		0.9250	0.4428	0.0461
200mg vs. NP: p=		0.8750	0.7674	0.3272

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A.2 Statistical analyses for study N49-96-02-021

Table A.16 Patient disposition- N49-96-02-021

	Placebo	SC-58635 50mg BID	SC-58635 100mg BID	SC-58635 200mg BID	NAPROXEN 500mg BID	Total
Randomized	242	252	239	233	226	1192
Week 12	119	168	165	154	147	
ITT	242	252	239	233	226	1192

A.2.1 Primary variables- primary analyses

**Table A.17 Primary variable: Patients global assessment of Arthritis
mean change from baseline--study N49-96-02-021**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	242	-0.6651	-0.7583	-0.6814
50 mg	252	-0.9795	-1.0542	-0.9979
100 mg	239	-1.0425	-1.0417	-0.9507
200 mg	233	-1.1367	-1.1245	-1.0804
Naproxen (NP)	226	-1.1840	-1.2078	-1.1111
Contrast				
100mg vs. PL: p=		0.0001	0.0015	0.0032
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.2317	0.3569	0.1575
100mg vs. NP: p=		0.0751	0.0671	0.0832
200mg vs. NP: p=		0.5543	0.3613	0.7419

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NDA 20-998 Celecoxib (SC-58635)

Table A.18 Primary variable: Physician's global assessment of Arthritis
mean change from baseline--study N49-96-02-021

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	242	-0.6326	-0.7094	-0.6644
50 mg	252	-0.9157	-1.0005	-1.0089
100 mg	239	-0.9614	-1.0098	-0.9858
200 mg	233	-1.0695	-1.0356	-1.0216
Naproxen (NP)	226	-1.1188	-1.1964	-1.1078
Contrast				
100mg vs. PL: p=		0.0001	0.0003	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.1521	0.7553	0.6657
100mg vs. NP: p=		0.0388	0.0256	0.1449
200mg vs. NP: p=		0.5204	0.0561	0.3067

Table A.19 Primary variable: Patients' assessment of Pain (VAS)
mean change from baseline--study N49-96-02-021

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	242	-12.9351	-14.5968	-11.9606
50 mg	252	-21.4726	-21.7162	-20.2688
100 mg	239	-20.3037	-21.7429	-19.6386
200 mg	233	-26.4443	-24.1312	-21.0025
Naproxen (NP)	226	-26.5621	-24.9980	-25.3095
Contrast				
100mg vs. PL: p=		0.0006	0.0023	0.0012
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.0045	0.3121	0.5674
100mg vs. NP: p=		0.0041	0.1726	0.0187
200mg vs. NP: p=		0.9571	0.7177	0.0753

Table A.20 Primary variable: Womac composite score
mean change from baseline--study N49-96-02-021

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 12	
Placebo (PL)	240	-4.9853	-5.4287	
50 mg	247	-10.3067	-12.8876	
100 mg	237	-11.7026	-11.9927	
200 mg	230	-12.1559	-11.5236	
Naproxen (NP)	225	-12.6084	-13.9321	
Contrast				
100mg vs. PL: p=		0.0001	0.0001	
200mg vs. PL : p=		0.0001	0.0001	
100mg vs. 200mg: p=		0.7203	0.7514	
100mg vs. NP: p=		0.4771	0.1933	
200mg vs. NP: p=		0.7246	0.1091	

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Table A.21 Primary variable: Womac pain score
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	242	-1.2028	-1.3588
50 mg	248	-2.1322	-2.7939
100 mg	237	-2.3993	-2.5667
200 mg	232	-2.6182	-2.5282
Naproxen (NP)	226	-2.8409	-3.0053
Contrast			
100mg vs. PL: p=		0.0001	0.0003
200mg vs. PL : p=		0.0001	0.0005
100mg vs. 200mg: p=		0.4513	0.9090
100mg vs. NP: p=		0.1317	0.1971
200mg vs. NP: p=		0.4501	0.1634

Table A.22 Primary variable: Womac joint stiffness
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	242	-0.5815	-0.5059
50 mg	248	-0.9079	-1.1926
100 mg	237	-1.0004	-1.1022
200 mg	232	-1.1395	-1.0918
Naproxen (NP)	226	-1.2022	-1.2612
Contrast			
100mg vs. PL: p=		0.0013	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.2901	0.9418
100mg vs. NP: p=		0.1280	0.2724
200mg vs. NP: p=		0.6375	0.2443

Table A.23 Primary variable: Womac physical functions
mean change from baseline--study N49-96-02-021

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 12
Placebo (PL)	240	-3.2340	-3.5925
50 mg	250	-7.2830	-8.8585
100 mg	237	-8.3051	-8.3216
200 mg	231	-8.3940	-7.8901
Naproxen (NP)	225	-8.5207	-9.6258
Contrast			
100mg vs. PL: p=		0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.9236	0.6881
100mg vs. NP: p=		0.8174	0.2285
200mg vs. NP: p=		0.8928	0.1116

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NDA 20-998 Celecoxib (SC-58635)

Table A.24 Primary variable: Patients global assessment of Arthritis
categorical change from baseline--study N49-96-02-021

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	242	39 (16.1%)	193 (79.8%)	10 (4.1%)	61 (25.2%)	163 (67.4%)	18 (7.4%)	54 (22.3%)	169 (69.8%)	19 (7.9%)
50 mg	252	68 (27%)	176 (69.8%)	8 (3.2%)	91 (36.1%)	151 (59.9%)	10 (4%)	85 (33.7%)	155 (61.5%)	12 (4.8%)
100 mg	239	73 (30.5%)	161 (67.4%)	5 (2.1%)	84 (35.2%)	150 (62.8%)	5 (2.1%)	75 (31.4%)	157 (65.7%)	7 (2.9%)
200 mg	233	79 (33.9%)	150 (64.4%)	4 (1.7%)	87 (37.3%)	140 (60.1%)	6 (2.6%)	84 (36.1%)	140 (60.1%)	9 (3.9%)
Naproxen (NP)	226	81 (35.8%)	144 (63.7%)	1 (0.4%)	87 (38.5%)	135 (59.7%)	4 (1.8%)	83 (36.7%)	138 (61.1%)	5 (2.2%)
pairwise comparison										
100mg vs. PL		p= 0.001				p= 0.003				p= 0.005
200mg vs. PL		p= 0.001				p= 0.001				p= 0.001
100mg vs. 200mg		p=0.418				p=0.685				p=0.386
100mg vs. NP		p=0.153				p=0.443				p=0.207
200mg vs. NP		p=0.542				p=0.724				p=0.712

*Imp=Improved, Nchg=No change, Wors=worsened

Table A.25 Primary variable: Physician's global assessment of Arthritis
categorical change from baseline--study N49-96-02-021

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	242	42 (17.4%)	188 (77.7%)	12 (5%)	52 (21.5%)	175 (72.3%)	15 (6.2%)	50 (20.7%)	177 (73.1%)	15 (6.2%)
50 mg	252	59 (23.4%)	187 (74.2%)	6 (2.4%)	78 (31%)	167 (66.3%)	7 (2.8%)	80 (31.8%)	165 (65.5%)	7 (2.8%)
100 mg	239	65 (27.2%)	172 (72%)	2 (0.8%)	75 (31.4%)	161 (61.4%)	3 (1.3%)	73 (30.5%)	162 (67.8%)	4 (1.7%)
200 mg	232	70 (30.2%)	159 (68.5%)	3 (1.3%)	75 (32.3%)	153 (66%)	4 (1.7%)	72 (31%)	155 (66.8%)	5 (2.2%)
Naproxen (NP)	226	74 (32.7%)	152 (67.3%)	0 (0%)	86 (38.1%)	139 (61.5%)	1 (0.4%)	77 (34.1%)	148 (65.5%)	1 (0.4%)
pairwise comparison										
100mg vs. PL		p= 0.001				p= 0.002				p= 0.002
200mg vs. PL		p= 0.001				p= 0.001				p= 0.002
100mg vs. 200mg		p=0.535				p=0.888				p=0.973
100mg vs. NP		p=0.153				p=0.109				p=0.325
200mg vs. NP		p=0.432				p=0.150				p=0.350

*Imp=Improved, Nchg=No change, Wors=worsened

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A.2.2 Secondary Variables

Table A.26 Secondary variable: Patients' withdrawal due to lack of efficacy
study N49-96-02-021

	withdrawal due to lack of efficacy		pairwise comparison
	Yes	No	
Treatment	N (%)	N (%)	
Placebo (PL)	89 (36.8%)	153 (63.2%)	100mg vs. PL: p= 0.001
50 mg	56 (22.2%)	196 (77.8%)	200mg vs. PL : p= 0.002
100 mg	51 (21.3%)	188 (78.7%)	100mg vs. 200mg: p=0.935
200 mg	49 (21%)	184 (79%)	100mg vs. NP: p=0.323
Naproxen (NP)	40 (17.7%)	186 (82.3%)	200mg vs. NP: p=0.367

Table A.27 Secondary variable: Time to withdrawal due to lack of efficacy
study N49-96-02-021

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	89 (36.8%)	53.45 (1.70)	100mg vs. PL: p= 0.0001
50 mg	56 (22.2%)	58.04 (1.18)	200mg vs. PL : p= 0.0002
100 mg	51 (21.3%)	60.64 (1.26)	100mg vs. 200mg: p=0.8698
200 mg	49 (21%)	66.82 (1.29)	100mg vs. NP: p=0.3672
Naproxen (NP)	40 (17.7%)	65.52 (1.19)	200mg vs. NP: p=0.4656

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Table A.28 Secondary variable: APS Pain scale—Total score change from baseline--study N49-96-02-021

Treatment	N	day 1	day 2	day3	day4	day5	day 6	day 7
Placebo (PL)	169	-3.24	-2.84	-3.36	-3.14	-4.02	-4.71	-4.65
50 mg	171	-4.15	-5.55	-6.58	-7.27	-8.17	-8.12	-8.90
100 mg	165	-3.93	-5.58	-7.12	-8.45	-9.26	-9.59	-9.80
200 mg	159	-4.85	-6.98	-9.00	-10.0	-10.61	-11.42	-11.41
Naproxen (NP)	170	-4.15	-6.97	-8.43	-9.14	-10.07	-10.67	-11.12
Contrast								
100mg vs. PL: p=	0.5540	0.0379	0.0068	0.0002	0.0003	0.0009	0.0007	
200mg vs. PL : p=	0.1718	0.0018	0.0001	0.0001	0.0001	0.0001	0.0001	
100mg vs. 200mg: p=	0.4424	0.2977	0.1832	0.2829	0.3542	0.2210	0.2936	
100mg vs. NP: p=	0.8498	0.2910	0.3405	0.6251	0.5693	0.4627	0.3786	
200mg vs. NP: p=	0.5574	0.9937	0.6884	0.5488	0.7099	0.6108	0.8494	

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A.2.3 Supportive variables:

Table A.29 Supportive variable: Functional capacity classification
mean change from baseline--study N49-96-02-021

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	242	-0.0702	-0.0676	-0.0596
50 mg	252	-0.1470	-0.1709	-0.1587
100 mg	239	-0.1409	-0.1743	-0.1452
200 mg	233	-0.1638	-0.1700	-0.1511
Naproxen (NP)	226	-0.1523	-0.1801	-0.1983
Contrast				
100mg vs. PL: p=		0.0265	0.0021	0.0149
200mg vs. PL : p=		0.0035	0.0033	0.0096
100mg vs. 200mg: p=		0.4769	0.9010	0.8682
100mg vs. NP: p=		0.7254	0.8700	0.1369
200mg vs. NP: p=		0.7253	0.7754	0.1881

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Table A.30 Supportive variable: Osteoarthritis severity index
mean change from baseline--study N49-96-02-021

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	242	-1.6331	-2.0256	-1.8696
50 mg	252	-2.5995	-3.3148	-3.3546
100 mg	238	-2.7644	-3.2627	-2.9097
200 mg	233	-3.2425	-3.5425	-3.3177
Naproxen (NP)	226	-3.2944	-4.1611	-3.6957
Contrast				
100mg vs. PL: p=		0.0002	0.0002	0.0029
200mg vs. PL : p=		0.0001	0.0005	0.0001
100mg vs. 200mg: p=		0.1201	0.4316	0.2454
100mg vs. NP: p=		0.0878	0.0125	0.0267
200mg vs. NP: p=		0.8681	0.0869	0.2889

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A.3 Statistical analyses for study N49-96-02-054

Table A.31 Patient disposition- N49-96-02-054

	Placebo	SC-58635 50mg BID	SC-58635 100mg BID	SC-58635 200mg BID	NAPROXEN 500mg BID	Total
Randomized	217	216	207	213	207	1060
Week 12	79	111	111	119	118	
ITT	217	216	207	213	207	1060

A.3.1 Primary variables- primary analyses

**Table A.32 Primary variable: Patients global assessment of Arthritis
mean change from baseline--study N49-96-02-054**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	217	-0.6065	-0.5781	-0.5213
50 mg	216	-0.9316	-1.0197	-0.9269
100 mg	207	-1.1649	-1.1207	-1.0673
200 mg	213	-1.1082	-1.1012	-0.9292
Naproxen (NP)	207	-1.1949	-1.1043	-1.1256
Contrast				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.4840	0.8320	0.1456
100mg vs. NP: p=		0.7120	0.8593	0.5415
200mg vs. NP: p=		0.2846	0.9731	0.0389

**Table A.33 Primary variable: Physician's global assessment of Arthritis
mean change from baseline--study N49-96-02-054**

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	217	-0.6381	-0.6304	-0.5901
50 mg	216	-0.9189	-1.0612	-0.9818
100 mg	207	-1.0867	-1.0715	-1.0420
200 mg	213	-1.0684	-1.1214	-0.9705
Naproxen (NP)	207	-1.1016	-1.0694	-1.0750
Contrast				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.8148	0.5706	0.4266
100mg vs. NP: p=		0.8498	0.9814	0.7148
200mg vs. NP: p=		0.6712	0.5549	0.2453

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Table A.34 Primary variable: Patients' assessment of Pain (VAS)
mean change from baseline--study N49-96-02-054

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 6	week 12
Placebo (PL)	217	-11.8009	-13.2092	-11.1376
50 mg	216	-19.6990	-21.4598	-18.9751
100 mg	207	-24.3893	-25.0731	-23.2957
200 mg	213	-24.4477	-23.8946	-19.3496
Naproxen (NP)	207	-26.5364	-24.7886	-22.2511
Contrast				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0012
100mg vs. 200mg: p=		0.9796	0.6358	0.1235
100mg vs. NP: p=		0.3498	0.9095	0.6850
200mg vs. NP: p=		0.3605	0.7195	0.2574

Table A.35 Primary variable: Womac composite score
mean change from baseline--study N49-96-02-054

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 12	
Placebo (PL)	217	-3.3653	-4.6050	
50 mg	214	-7.6257	-8.0025	
100 mg	207	-11.6808	-10.2635	
200 mg	211	-11.6437	-10.8441	
Naproxen (NP)	205	-12.7083	-12.3809	
Contrast				
100mg vs. PL: p=		0.0001	0.0001	
200mg vs. PL : p=		0.0001	0.0001	
100mg vs. 200mg: p=		0.9764	0.6814	
100mg vs. NP: p=		0.4166	0.1372	
200mg vs. NP: p=		0.3987	0.2792	

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Table A.36 Primary variable: Womac pain score
mean change from baseline--study N49-96-02-054

		Change from Baseline (least square mean)		
Treatment	N	week 2	week 12	
Placebo (PL)	217	-0.7217	-0.9835	
50 mg	215	-1.7759	-1.6781	
100 mg	207	-2.6096	-2.2333	
200 mg	211	-2.5371	-2.4038	
Naproxen (NP)	207	-2.8593	-2.6814	
Contrast				
100mg vs. PL: p=		0.0001	0.0002	
200mg vs. PL : p=		0.0001	0.0001	
100mg vs. 200mg: p=		0.8041	0.6072	
100mg vs. NP: p=		0.3944	0.1787	
200mg vs. NP: p=		0.2706	0.4032	

Table A.36 Primary variable: Womac joint stiffness
mean change from baseline--study N49-96-02-054

		Change from Baseline (least square mean)	
Treatment	N	week 2	week 12
Placebo (PL)	217	-0.2940	-0.4128
50 mg	216	-0.7510	-0.8079
100 mg	207	-1.0140	-1.0074
200 mg	211	-1.0312	-1.0145
Naproxen (NP)	205	-1.1033	-1.1367
Contrast			
100mg vs. PL: p=		0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.8955	0.9593
100mg vs. NP: p=		0.4984	0.3540
200mg vs. NP: p=		0.5836	0.3795

Table A.37 Primary variable: Womac physical functions
mean change from baseline--study N49-96-02-054

		Change from Baseline (least square mean)	
Treatment	N	week 2	week 12
Placebo (PL)	217	-2.3261	-3.1682
50 mg	215	-5.4474	-5.4793
100 mg	207	-8.0330	-6.9910
200 mg	211	-8.0963	-7.5191
Naproxen (NP)	207	-8.7029	-8.4480
Contrast			
100mg vs. PL: p=		0.0001	0.0002
200mg vs. PL : p=		0.0001	0.0001
100mg vs. 200mg: p=		0.9453	0.6088
100mg vs. NP: p=		0.4698	0.1600
200mg vs. NP: p=		0.5114	0.3687

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**Table A.38 Primary variable: Patients global assessment of Arthritis
categorical change from baseline--study N49-96-02-054**

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	217	35 (16.1%)	171 (78.8%)	11 (5.1%)	38 (17.5%)	162 (74.7%)	17 (7.8%)	36 (16.6%)	164 (75.6%)	17 (7.8%)
50 mg	216	51 (23.6%)	160 (74.1%)	5 (2.3%)	67 (31%)	143 (66.2%)	6 (2.8%)	56 (25.9%)	153 (70.8%)	7 (3.2%)
100 mg	207	67 (32.4%)	137 (66.2%)	3 (1.5%)	71 (34.3%)	131 (63.3%)	5 (2.4%)	65 (31.4%)	137 (66.2%)	5 (2.4%)
200 mg	213	75 (35.2%)	132 (62%)	6 (2.8%)	78 (36.6%)	126 (59.2%)	9 (4.2%)	61 (28.6%)	142 (66.7%)	10 (4.7%)
Naproxen (NP)	207	66 (31.9%)	138 (66.7%)	3 (1.5%)	63 (30.4%)	139 (67.2%)	5 (2.4%)	70 (33.8%)	131 (63.3%)	6 (2.9%)
pairwise comparison										
100mg vs. PL		p= 0.001				p= 0.001				p= 0.001
200mg vs. PL		p= 0.001				p= 0.001				p= 0.002
100mg vs. 200mg		p=0.690				p=0.823				p=0.360
100mg vs. NP		p=0.919				p=0.424				p=0.669
200mg vs. NP		p=0.618				p=0.315				p=0.186

*Imp=Improved, Nchg=No change, Wors=worsened

**Table A.39 Primary variable: Physician's global assessment of Arthritis
categorical change from baseline--study N49-96-02-054**

Treatment	N	week 2			week 6			week 12		
		Imp*	Nchg	Wors	Imp	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	217	37 (17.1%)	172 (79.3%)	8 (3.7%)	42 (19.4%)	166 (76.5%)	9 (4.2%)	39 (18%)	169 (77.9%)	9 (4.2%)
50 mg	216	55 (25.5%)	158 (73.2%)	3 (1.4%)	68 (31.5%)	144 (66.7%)	4 (1.9%)	59 (27.3%)	152 (70.4%)	5 (2.3%)
100 mg	207	60 (29%)	145 (70.1%)	2 (1%)	70 (33.8%)	135 (65.2%)	2 (1%)	66 (31.9%)	139 (67.2%)	2 (1%)
200 mg	213	69 (32.4%)	140 (65.7%)	4 (1.9%)	80 (37.6%)	128 (60.1%)	5 (2.4%)	63 (29.6%)	145 (68.1%)	5 (2.4%)
Naproxen (NP)	207	63 (30.4%)	141 (68.1%)	3 (1.5%)	63 (30.4%)	139 (67.2%)	5 (2.4%)	66 (31.9%)	136 (65.7%)	5 (2.4%)
pairwise comparison										
100mg vs. PL		p= 0.001				p= 0.001				p= 0.001
200mg vs. PL		p= 0.001				p= 0.001				p= 0.003
100mg vs. 200mg		p=0.551				p=0.557				p=0.482
100mg vs. NP		p=0.811				p=0.357				p=0.832
200mg vs. NP		p=0.724				p=0.139				p=0.633

*Imp=Improved, Nchg=No change, Wors=worsened

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A3.2 Secondary Variables

Table A.40 Secondary variable: Patients' withdrawal due to lack of efficacy
study N49-96-02-054

	withdrawal due to lack of efficacy		
	Yes	No	pairwise comparison
Treatment	N (%)	N (%)	
Placebo (PL)	112 (51.6%)	105 (48.4%)	100mg vs. PL: p= 0.001
50 mg	76 (35.2%)	140 (64.8%)	200mg vs. PL : p= 0.001
100 mg	61 (29.5%)	146 (70.5%)	100mg vs. 200mg: p=0.404
200 mg	55 (25.8%)	158 (74.2%)	100mg vs. NP: p=0.269
Naproxen (NP)	51 (24.6%)	156 (75.4%)	200mg vs. NP: p=0.780

Table A.41 Secondary variable: Time to withdrawal due to lack of efficacy
study N49-96-02-054

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	112 (51.6%)	42.9 (1.89)	100mg vs. PL: p= 0.0001
50 mg	76 (35.2%)	58.5 (1.95)	200mg vs. PL : p= 0.0001
100 mg	61 (29.5%)	57.9 (1.54)	100mg vs. 200mg: p=0.5444
200 mg	55 (25.8%)	56.5 (1.46)	100mg vs. NP: p=0.3690
Naproxen (NP)	51 (24.6%)	60.9 (1.61)	200mg vs. NP: p=0.7719

Table A.42 Secondary variable: APS Pain scale—Total score
mean change from baseline--study N49-96-02-054

Treatment	N	day 1	day 2	day3	day4	day5	day 6	day 7
Placebo (PL)	212	-1.33	-2.37	-2.99	-3.48	-2.55	-3.07	-3.76
50 mg	211	-3.49	-5.64	-7.62	-8.49	-8.79	-8.75	-9.28
100 mg	205	-4.41	-7.68	-8.76	-9.05	-9.67	-9.59	-10.11
200 mg	206	-4.43	-8.30	-10.09	-11.79	-12.04	-12.19	-12.71
Naproxen (NP)	202	-5.10	-8.53	-10.23	-11.69	12.53	-13.20	-13.24
Contrast								
100mg vs. PL: p=		0.0013	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0012	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.9808	0.5679	0.2573	0.0226	0.0566	0.0430	0.0502
100mg vs. NP: p=		0.4719	0.4355	0.2117	0.0291	0.0222	0.0053	0.0190
200mg vs. NP: p=		0.4863	0.8321	0.9026	0.9311	0.6954	0.4360	0.6890

A.3.3 Supportive variables:

**Table A.43 Supportive variable: Functional capacity classification
mean change from baseline--study N49-96-02-054**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	217	-0.0848	-0.0811	-0.0541
50 mg	216	-0.1462	-0.1999	-0.1680
100 mg	207	-0.1444	-0.1818	-0.1787
200 mg	213	-0.1576	-0.1769	-0.1388
Naproxen (NP)	207	-0.1667	-0.1708	-0.1782
Contrast				
100mg vs. PL: p=		0.0797	0.0075	0.0013
200mg vs. PL : p=		0.0309	0.0103	0.0269
100mg vs. 200mg: p=		0.6991	0.8979	0.3030
100mg vs. NP: p=		0.5158	0.7722	0.9892
200mg vs. NP: p=		0.7888	0.8704	0.3096

**Table A.44 Supportive variable: Osteoarthritis severity index
mean change from baseline--study N49-96-02-054**

Treatment	N	Change from Baseline (least square mean)		
		week 2	week 6	week 12
Placebo (PL)	215	-1.4542	-1.7450	-1.4957
50 mg	216	-2.5635	-3.3241	-2.7100
100 mg	207	-3.6189	-3.8207	-3.7520
200 mg	212	-3.0516	-3.7315	-3.0864
Naproxen (NP)	206	-3.3079	-3.5016	-3.0947
Contrast				
100mg vs. PL: p=		0.0001	0.0001	0.0001
200mg vs. PL : p=		0.0001	0.0001	0.0001
100mg vs. 200mg: p=		0.0709	0.8060	0.0688
100mg vs. NP: p=		0.3258	0.3834	0.0746
200mg vs. NP: p=		0.4160	0.5283	0.9819

A.4 Statistical analyses for study N49-96-02-060

Table A.45 Patient disposition- N49-96-02-060

	Placebo	SC-58635 100mg BID	SC-58635 200mg QD	Total
Randomized	232	231	223	686
Week 2	186	213	210	609
Week 6	146	194	182	522
ITT	231	231	222	684

A.4.1 Primary variables- primary analyses

Table A.46 Primary variable: Patients global assessment of Arthritis
mean change from baseline--study N49-96-02-060

		Change from Baseline (least square mean)	
Treatment	N	week 2	week 6
Placebo (PL)	231	-0.7782	-0.8337
100 mg BID	231	-1.2456	-1.3102
200 mg QD	222	-1.2661	-1.3156
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.8087	0.9537

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Table A.47 Primary variable: Physician's global assessment of Arthritis
mean change from baseline--study N49-96-02-060

Treatment	N	week 2	week 6
Placebo (PL)	231	-0.7766	-0.8233
100 mg BID	231	-1.2733	-1.3102
200 mg QD	222	-1.2832	1.3249
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.9006	0.8659

Table A.48 Primary variable: Patients' assessment of Pain (VAS)
mean change from baseline--study N49-96-02-060

Treatment	N	week 2	week 6
Placebo (PL)	231	-12.8962	-14.7662
100 mg BID	231	-25.5027	-28.4604
200 mg QD	222	-26.1202	-27.6791
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.7796	0.7473

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**Table A.49 Primary variable: Womac scores
mean change from baseline at week 6--study N49-96-02-060**

Treatment	Variables			
	composite (N)	pain (N)	joint stiffness (N)	physical functions (N)
Placebo (PL)	-6.638 (229)	-1.490 (231)	-0.572 (230)	-4.496 (230)
100 mg BID	-14.055 (229)	-3.099(230)	-1.220 (230)	-9.683 (229)
200 mg QD	-12.830 (219)	-2.872 (220)	-1.165 (220)	-8.771 (219)
Contrast				
100mg BID vs. PL: p=	0.0001	0.0001	0.0001	0.0001
200mg QD vs. PL : p=	0.0001	0.0001	0.0001	0.0001
100mg BID vs. 200mg QD : p=	0.3853	0.4730	0.6953	0.3805

**Table A.50 Primary variable: Patients global assessment of Arthritis
categorical change from baseline--study N49-96-02-060**

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	231	52 (22.5%)	168 (72.7%)	11 (4.8%)	59 (25.5%)	161 (69.7%)	11 (4.8%)
100 mg	231	88 (38.1%)	141 (61%)	2 (0.9%)	98 (42.4%)	131 (56.7%)	2 (0.9%)
200 mg	222	85 (38.3%)	135 (60.8%)	2 (0.9%)	94 (42.3%)	120 (54.1%)	8 (3.6%)
pairwise comparison							
100mg BID vs. PL: p=		p= 0.001			p= 0.001		
200mg QD vs. PL : p=		p= 0.001			p= 0.001		
100mg BID vs. 200mg QD : p=		p=0.971			p=0.725		

*Imp=Improved, Nchg=No change, Wors=worsened

**Table A.51 Primary variable: Physician's global assessment of Arthritis
categorical change from baseline--study N49-96-02-060**

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	231	48 (20.8%)	174 (75.3%)	9 (3.9%)	57 (24.7%)	165 (71.4%)	9 (3.9%)
100 mg	231	89 (38.5%)	141 (61%)	1 (0.4%)	100 (43.3%)	130 (56.3%)	1 (0.4%)
200 mg	222	91 (41%)	130 (58.6%)	1 (0.5%)	95 (42.8%)	123 (55.4%)	4 (1.8%)
pairwise comparison							
100mg BID vs. PL: p=		p= 0.001			p= 0.001		
200mg QD vs. PL : p=		p= 0.001			p= 0.001		
100mg BID vs. 200mg QD : p=		p=0.597			p=0.786		

*Imp=Improved, Nchg=No change, Wors=worsened

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A.4.2 Secondary Variables

Table A.52 Secondary variable: Patients' withdrawal due to lack of efficacy study N49-96-02-060

	withdrawal due to lack of efficacy		
	Yes	No	pairwise comparison
Treatment	N (%)	N (%)	
Placebo (PL)	56 (24.2%)	175 (75.8%)	100mg BID vs. PL: p= 0.001
100 mg BID	18 (7.8%)	213 (92.2%)	200mg QD vs. PL: p= 0.001
200 mg QD	21 (9.5%)	201 (90.5%)	100mg BID vs. 200mg QD : p=0.528

Table A.53 Secondary variable: Time to withdrawal due to lack of efficacy study N49-96-02-060

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	56 (24.2%)	24.9 (0.52)	100mg BID vs. PL: p= 0.0001
100 mg	18 (7.8%)	26.9 (0.29)	200mg QD vs. PL: p= 0.0001
200 mg	21 (9.5%)	32.2 (0.42)	100mg BID vs. 200mg QD : p=0.4780

A.4.3 Supportive variables:

Table A.54 Supportive variable: Functional capacity classification mean change from baseline--study N49-96-02-060

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	231	-0.0809	-0.1061
100 mg BID	231	-0.1945	-0.1543
200 mg QD	222	-0.1651	-0.1442
Contrast			
100mg BID vs. PL: p=		0.0013	0.1695
200mg QD vs. PL : p=		0.0180	0.2808
100mg BID vs. 200mg QD : p=		0.4100	0.7767

Table A.55 Supportive variable: Osteoarthritis severity index mean change from baseline--study N49-96-02-060

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	231	-2.1802	-2.4225
100 mg BID	231	-4.0974	-3.9485
200 mg QD	222	-3.8164	-4.1540
Contrast			
100mg BID vs. PL: p=		0.0001	0.0001
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD : p=		0.4151	0.5683

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A.5 Statistical analyses for study N49-96-02-087

Table A.56 Patient disposition- N49-96-02-087

	Placebo	SC-58635 100mg BID	SC-58635 200mg QD	Total
Randomized	244	243	231	718
Week 2	207	227	218	652
Week 6	164	194	191	549
ITT	243	241	231	715

A.5.1 Primary variables- primary analyses

Table A.56 Primary variable: Patients global assessment of Arthritis
mean change from baseline--study N49-96-02-087

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	243	-0.7774	-0.8215
100 mg BID	241	-1.1282	-1.0598
200 mg QD	231	-1.1245	-1.1946
Contrast			
100mg BID vs. PL: p=		0.0001	0.0077
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.9625	0.1355

Table A.57 Primary variable: Physician's global assessment of Arthritis
mean change from baseline--study N49-96-02-087

Treatment	N	week 2	week 6
Placebo (PL)	243	-0.7324	-0.7844
100 mg BID	241	-1.1235	-1.0318
200 mg QD	231	-1.0800	-1.1658
Contrast			
100mg BID vs. PL: p=		0.0001	0.0025
200mg QD vs. PL : p=		0.0001	0.0001
100mg BID vs. 200mg QD: p=		0.5525	0.1060

Table A.58 Primary variable: Patients' assessment of Pain (VAS)
mean change from baseline--study N49-96-02-087

Treatment	N	week 2	week 6
Placebo (PL)	243	-12.4032	-14.9532
100 mg BID	241	-22.4852	-21.1526
200 mg QD	231	-21.0834	-23.4803
Contrast			
100mg BID vs. PL: p=		0.0001	0.0107
200mg QD vs. PL : p=		0.0001	0.0006
100mg BID vs. 200mg QD: p=		0.5197	0.3441

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**Table A.59 Primary variable: Womac scores
mean change from baseline at week 6--study N49-96-02-087**

Treatment	Variables			
	composite (N)	pain (N)	joint stiffness (N)	physical functions (N)
Placebo (PL)	-8.098 (239)	-1.588 (239)	-0.780 (239)	-5.677 (240)
100 mg BID	-13.308 (238)	-2.596 (239)	-1.294 (240)	-9.361 (239)
200 mg QD	-13.934 (226)	-2.994 (226)	-1.197 (226)	-9.724 (226)
Contrast				
100mg BID vs. PL: p=	0.0011	0.0053	0.0004	0.0013
200mg QD vs. PL : p=	0.0003	0.0001	0.0050	0.0005
100mg BID vs. 200mg QD : p=	0.6983	0.2763	0.5093	0.7538

**Table A.60 Primary variable: Patients global assessment of Arthritis
categorical change from baseline--study N49-96-02-087**

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	243	56 (23.1%)	176 (72.4%)	11 (4.5%)	65 (26.8%)	160 (65.8%)	18 (7.4%)
100 mg	241	99 (41.1%)	137 (56.9%)	5 (2.1%)	90 (37.3%)	143 (59.3%)	8 (3.3%)
200 mg	231	71 (30.7%)	160 (69.3%)	0 (0%)	87 (37.7%)	143 (61.9%)	1 (0.4%)
pairwise comparison							
100mg BID vs. PL: p=		p= 0.001			p= 0.004		
200mg QD vs. PL : p=		p= 0.010			p= 0.001		
100mg BID vs. 200mg QD : p=		p=0.046			p=0.640		

*Imp=Improved, Nchg=No change, Wors=worsened

**Table A.61 Primary variable: Physician's global assessment of Arthritis
categorical change from baseline--study N49-96-02-087**

Treatment	N	week 2			week 6		
		Imp*	Nchg	Wors	Imp	Nchg	Wors
Placebo (PL)	243	47 (19.3%)	188 (77.4%)	8 (3.3%)	59 (24.3%)	172 (70.8%)	12 (4.9%)
100 mg	240	93 (38.8%)	144 (60%)	3 (1.3%)	84 (35%)	151 (62.9%)	5 (2.1%)
200 mg	231	66 (28.6%)	164 (71%)	1 (0.4%)	80 (34.6%)	151 (65.4%)	0 (0%)
pairwise comparison							
100mg BID vs. PL: p=		p= 0.001			p= 0.004		
200mg QD vs. PL : p=		p= 0.005			p= 0.002		
100mg BID vs. 200mg QD : p=		p=0.030			p=0.823		

*Imp=Improved, Nchg=No change, Wors=worsened

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A.5.2 Secondary Variables

Table A.62 Secondary variable: Patients' withdrawal due to lack of efficacy
study N49-96-02-087

	withdrawal due to lack of efficacy		
	Yes	No	pairwise comparison
Treatment	N (%)	N (%)	
Placebo (PL)	55 (22.6%)	188 (77.4%)	100mg BID vs. PL: p= 0.001
100 mg BID	27 (11.2%)	214 (88.8%)	200mg QD vs. PL: p= 0.001
200 mg QD	24 (10.4%)	207 (89.6%)	100mg BID vs. 200mg QD : p=0.776

Table A.63 Secondary variable: Time to withdrawal due to lack of efficacy
study N49-96-02-087

Treatment	Number of withdrawal N (%)	Time to withdrawal Mean (s.e.)	pairwise comparison (Log-rank test)
Placebo (PL)	55 (22.6%)	34 (0.76)	100mg BID vs. PL: p= 0.0006
100 mg	27 (11.2%)	30.2 (0.37)	200mg QD vs. PL: p= 0.0002
200 mg	24 (10.4%)	32.2 (0.39)	100mg BID vs. 200mg QD : p=0.7635

A.5.3 Supportive variables:

Table A.64 Supportive variable: Functional capacity classification mean change from baseline--study N49-96-02-087

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	243	-0.1125	-0.1248
100 mg BID	241	-0.1592	-0.1802
200 mg QD	231	-0.1573	-0.2003
Contrast			
100mg BID vs. PL: p=		0.1357	0.1286
200mg QD vs. PL : p=		0.1571	0.0408
100mg BID vs. 200mg QD : p=		0.9528	0.5857

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Table A.65. Supportive variable: Osteoarthritis severity index
mean change from baseline--study N49-96-02-087

Treatment	N	Change from Baseline (least square mean)	
		week 2	week 6
Placebo (PL)	243	-2.1231	-2.3701
100 mg BID	241	-3.7945	-3.6065
200 mg QD	230	-3.5535	-3.5918
Contrast			
100mg BID vs. PL: p=		0.0001	0.0005
200mg QD vs. PL : p=		0.0001	0.0007
100mg BID vs. 200mg QD : p=		0.4670	0.9675

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